Interference No. 105,358 **Paper No. ___**

Filed on behalf of Junior Party REDDY
By: Matthew I. Kreeger, Esq.
Morrison & Foerster LLP
425 Market Street
San Francisco, California 94105-2482
Telephone: (415) 268-7000
Facsimile: (415) 268-7522

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES
(Administrative Patent Judge Michael P. Tierney)

POLICE S. **REDDY**, SURESH K. TIKOO,
and LORNE A. BABIUK
(U.S. Patent No. 6,492,343)
Junior Party,

v.

MICHAEL A. **JOHNSON**, JEFFREY M. HAMMOND,
RICHARD J. McCOY and MICHAEL G. SHEPPARD
(U.S. Application No. 09/485,512)
Senior Party.

Patent Interference No. **105,358**
(Technology Center 1600)

REDDY SUBSTANTIVE MOTION 1
(to Change the Benefit Accorded Johnson for the Contested Subject Matters of Count 1 under 37 C.F.R. § 41.121(a)(1)(ii))

Johnson Exhibit _____
Reddy v. Johnson
Interference 105,538

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REDDY SUBSTANTIVE MOTION 1
(to Change the Benefit Accorded Johnson for the Contested Subject Matter of Count 1 under 37 C.F.R. § 41.121(a)(1)(ii))

I. REQUEST FOR RELIEF

Junior party REDDY, *et al.* ("Reddy") moves under 37 C.F.R. §§ 41.121(a)(1)(ii) and 41.208(a)(3) to change the benefit accorded Senior Party JOHNSON, *et al.* ("Johnson") with respect to Count 1. In particular, Reddy requests that Johnson be denied the benefit of the August 14, 1997 filing date of Australian Provisional Application No. PO 8560 ("the AU application") (Ex. 2003) because the application does not provide a constructive reduction to practice under 35 U.S.C. 102(g)(1) of an embodiment with the scope of Count 1.

If the Board grants this Motion, Reddy will become the Senior Party in this interference with respect to Count 1, based on the parties' respective dates of accorded constructive reductions to practice.

II. REASONS FOR RELIEF REQUESTED

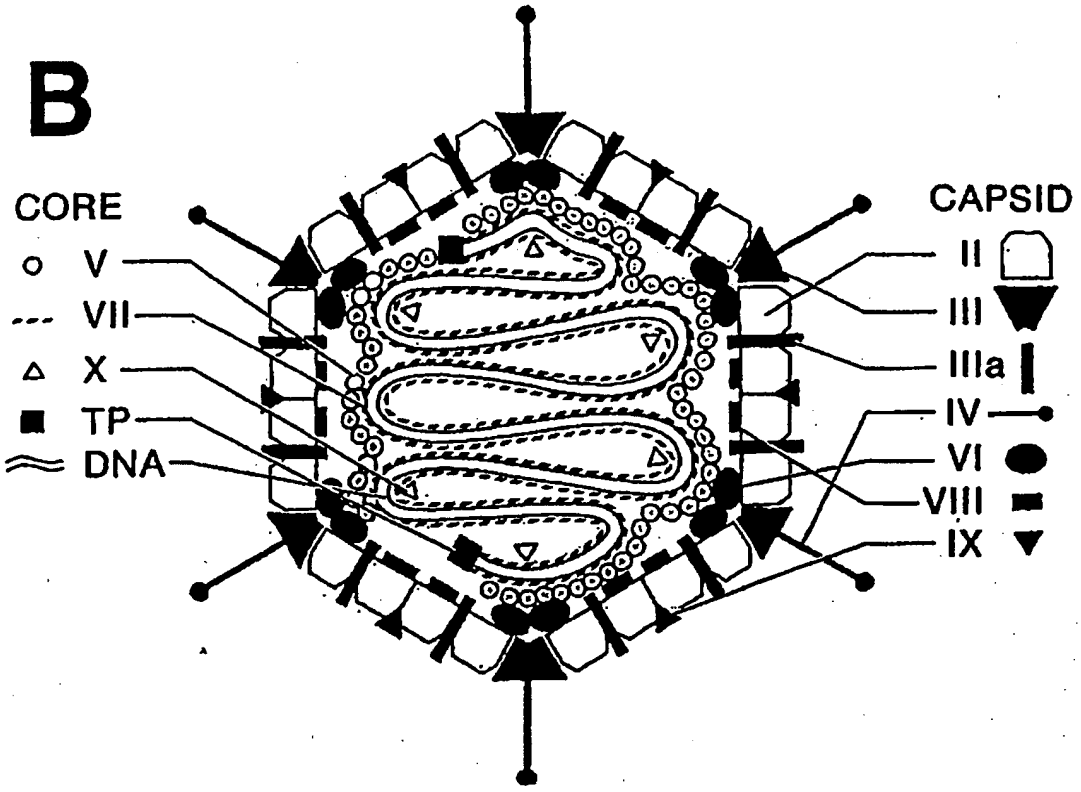
A. Background

The technology at issue in this interference relates to recombinant viruses that are engineered to be useful as vaccines. The particular viruses involved are porcine adenoviruses. An adenovirus is a DNA virus that infects the respiratory tract, intestines, and other mucous membranes. Fact ¶ 1. Adenoviruses are well-studied in humans, and are known to generate a strong immune response, though certain adenoviruses do not cause substantial harm to immunocompetent humans or animals. Fact ¶¶ 4, 6.

Adenoviruses infect a large variety of animals and birds. Fact ¶ 1. Known adenoviruses include human ("HAV"), porcine ("PAV"), bovine ("BAV"), mouse ("MAV"), and many others. Fact ¶ 1. Multiple strains, or "serotypes," of each of these types of adenoviruses are known to exist. These are referred to by number. Fact ¶ 2. For instance, human adenovirus serotype 2 is referred to as HAV2. Fact ¶ 3.

For nearly 20 years, scientists have recognized adenoviruses as having the potential to be recombined with foreign genes encoding antigens of more virulent pathogens for the purpose of creating vaccines. Fact ¶¶ 5,6. Since 1987, researchers have studied the potential use of adenoviruses as vectors for the delivery and expression of foreign DNA. Fact ¶ 5. One of the challenges that such scientists face is to insert the foreign genes (or "heterologous DNA") in such a way that the adenovirus retains the ability to replicate. Fact ¶ 35. In order to understand which regions of a given adenovirus are needed for replication, it is important to understand the life cycle of the adenovirus. Transcription of adenovirus DNA is accomplished in two phases: the early phase and the late phase. Fact ¶ 12. During the early phase, the virus selectively transcribes certain "early genes" that perform a variety of functions to create the necessary pre-conditions for viral replication. Fact ¶ 13. The adenovirus early genes are identified by number E1 through E4. Fact ¶ 14.

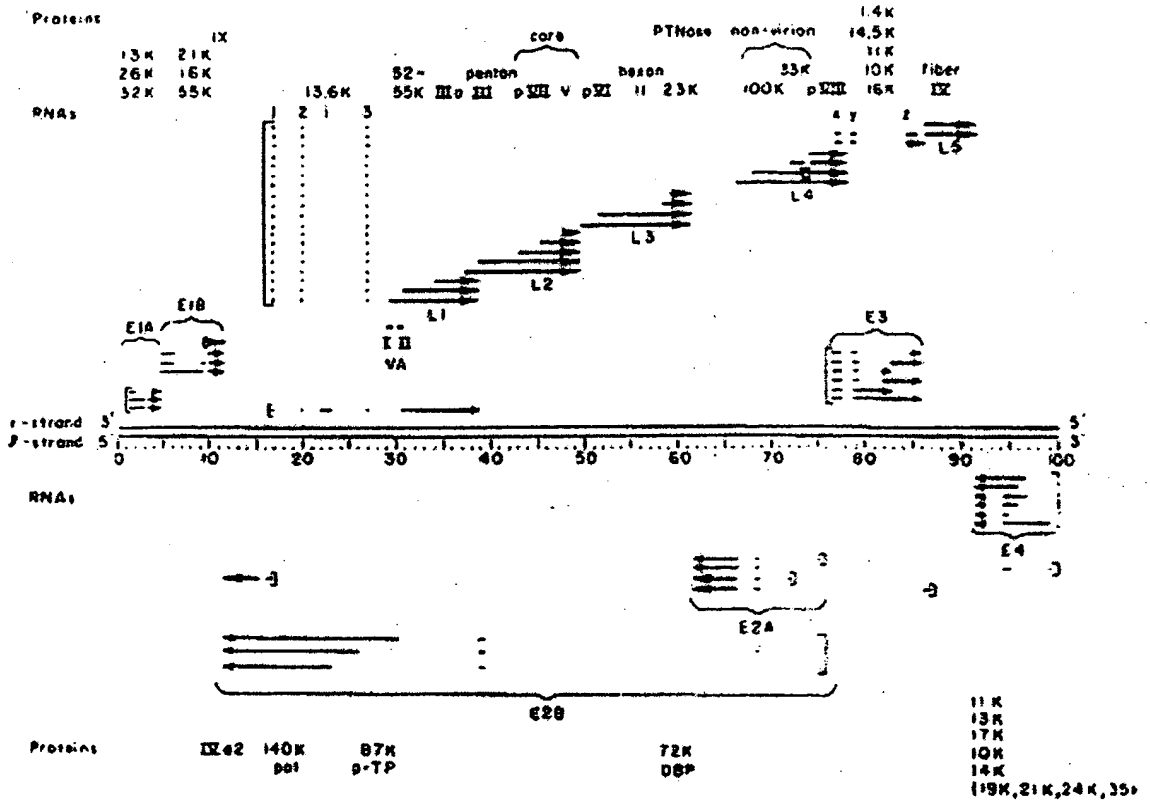
Once early-phase transcription is complete, transcription of the "late genes" may begin. Fact ¶ 15. The products of late genes include capsid proteins which are critical structural elements required for the virus to survive. Fact ¶¶ 8, 16. Adenoviruses have icosahedral capsids that are composed of proteins. Fact ¶ 7. By convention, adenovirus proteins are identified by Roman numerals, however the major capsid proteins are also known by other names such as "fiber" for pIV, "hexon" for pII, and "penton" for pIII. Fact ¶¶ 9, 10. The structure of HAV2, which is well studied in the art, is illustrated below:



Fact ¶ 7. Structural proteins, such as the pVIII protein, are products of late-phase transcription. Fact ¶ 31. Some early genes also encode polypeptides that are essential for viral replication. Fact ¶ 32. For instance, in human adenoviruses, E1 is essential for replication. Fact ¶ 39. Other early regions may be dispensable when the virus is to be grown in a cell culture in a laboratory. Fact ¶ 34.

Viral DNA is transcribed in blocks known as transcription units, which can be processed into multiple mRNAs. Fact ¶ 17. A single mRNA may consist of one or more "open reading frames," each of which can be translated into a protein. Fact ¶ 18. The open reading frame for one gene or protein may overlap with the open reading frame for another. Fact ¶ 19. As a result, the same sequence of nucleotides may form part of more than one gene and thus, more than one gene may be affected when a given sequence of nucleotides is deleted or recombined. Fact ¶ 20. The arrangement of genes or "open reading frames" on a viral genome is commonly illustrated in a "genome map," as

illustrated in the genome map of the human adenovirus serotype 2 (HAV2) reproduced below, as it was understood before August 1997:



Fact ¶¶ 21, 22. The E3 region of the HAV2 genome is shown to overlap with the L4 region, which the map associates with the gene for protein pVIII. Fact ¶ 29.

The genome map reproduced above employs the convention of "map units." Fact ¶ 23. A genome is "mapped" by dividing the whole genome into 100 units, shown in the x-axis of the map above. Fact ¶ 24. Thus, the specific point to which a given map unit (for example, 81) refers depends on the size of the genome. Fact ¶ 25. Map unit 81 refers to the 810th base in a genome of 1000 base, and to the 4,050th base in a genome of 5000 bases, for example. Fact ¶ 25. All of Johnson's claims in interference contain limitations directed towards insertions of heterologous DNA within certain map unit

ranges, although the only map unit range identified in the AU application (Ex. 2003) are map units 97-99.5. Fact ¶¶ 102, 120.

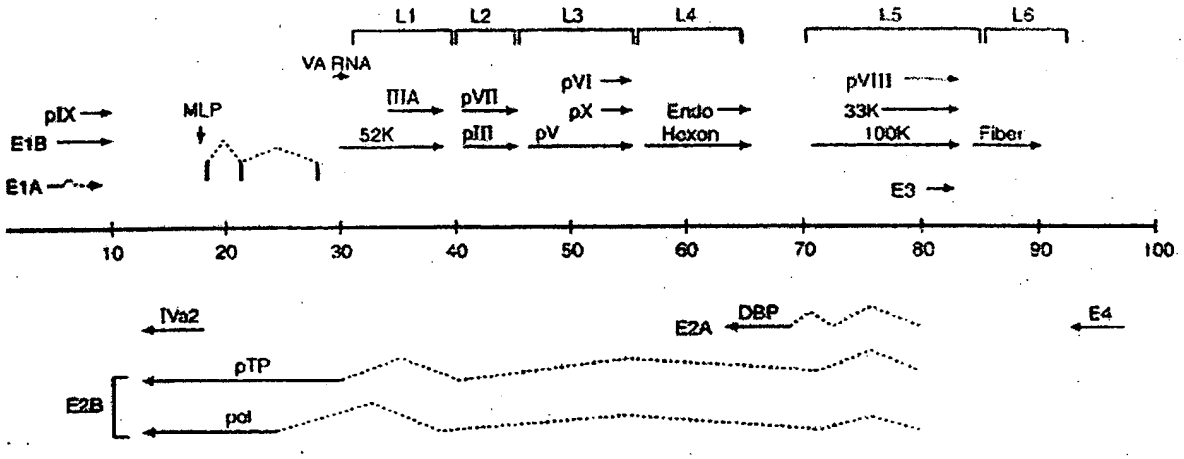
Adenoviruses have an upper limit to the amount of genetic information they can hold. Fact ¶ 46. For this reason, scientists working with recombinant adenoviruses are concerned with identifying ways to delete native DNA sequences in order to make room for foreign DNA sequences of interest. Fact ¶ 47. One way that this is accomplished is by identifying genes that encode products that are non-essential in viral replication Fact ¶¶ 40, 41. As is discussed below, this is the approach that Johnson used.

More difficult, but potentially more advantageous, is the approach of developing complementary cell lines that are customized to provide the elements that the virus needs to replicate. When such "helper" cell lines are available, the genes associated with the elements that the helper can produce are rendered superfluous for replication, and may be deleted to make room for foreign genes of interest. Fact ¶¶ 37, 38. This is among the approaches that Reddy employed, and the Reddy patent-in-interference in fact discloses such helper cell lines. Fact ¶ 39. If helper cell lines are available, it is possible – even desirable – to delete genes that are needed to make the virus replication-competent. Fact ¶ 47, 49. Deletions of native adenovirus DNA may prevent the expression of any genes that are associated with the deleted nucleotides. Fact ¶ 48.

At the time that the AU Application (Ex. 2003) was filed, no porcine serotype had yet been fully sequenced, and no PAV-3 genome map of the kind shown below on page 6 was available in the art. Fact ¶¶ 64, 65. Complete sequences for human adenovirus serotypes 2 and 5 were known. Fact ¶ 4. However, homology between human and porcine adenovirus sequences is limited, so the understanding in the art of human adenovirus suggested, at best, opportunities for further research. Fact ¶¶ 68-70. In addition, certain segments of the PAV3 genome had been sequenced. Specifically these included: pVIII, E3, E4, fibre, and the sequences of the late PAV3 genes encoding the structural proteins, penton, 100K and 23K. Fact ¶¶ 57-62. But the full PAV3 genome

sequence was not known, and the relationship of these regions to one another within the genome was not well-defined.

In 1998, Reddy (Ex. 2029) published for the first time a genome map of PAV3, reproduced below.



Fact ¶ 63. This genome map also employs the map unit convention. The arrows represent genes or groups of genes that are transcribed in PAV3. Fact ¶ 63. The bodies of the arrows show where the transcribed nucleotides are located, and the arrow heads identify the termination point of the genes. Fact ¶ 27. Above the line are genes that are transcribed left-to-right, and on the bottom are the genes that are transcribed right-to-left. Fact ¶ 63. Again, the illustration above shows, for example, that nucleotides encoding the E3 genes also encode the pVIII protein associated with late regions (specifically, the L5 region, in PAV3). Fact ¶ 86.

B. Count 1 of the Interference

Count 1 in interference is Claim 30 of the 09/485,512 application ("the '512 application") (Ex. 2002) or Claim 21 of Reddy United States Patent No. 6,492,343 ("the '343 patent") (Ex. 2001). Fact ¶ 98.

Claim 30 of the '512 application ("Johnson Claim 30") corresponds to the claim:

> A recombinant vector including a recombinant porcine adenovirus stably incorporating, and expressing heterologous DNA wherein said heterologous DNA is stably integrated into the adenovirus E3 region of the genome at map units from about 81 to about 84 of PAV3

('512 application, Ex. 2002.) Fact ¶ 99.

Claim 21 of the '343 patent ("Reddy Claim 21") corresponds to the claim:

> A recombinant PAV-3 vector comprising a PAV-3 genome capable of duplex formation under conditions of high stringency to the PAV-3 genome as depicted in SEQ ID NO:1, or a complement thereof and at least one heterologous nucleotide sequence, wherein the heterologous nucleotide sequence is inserted in the E3 region.

('343 patent, Ex. 2001.) Fact ¶ 100.

In the Notice Declaring Interference (Ex. 2005), Johnson was accorded benefit of the Johnson PCT patent application No. PCT/AU98/00648, filed August 14, 1998 (Ex. 2004); and Australian application No. PO 8560, filed August 14, 1997 (Ex. 2003), for both Counts 1 and 2. Fact ¶ 101.

C. The Disclosures in the AU application

The earliest priority document to which Johnson has been accorded benefit is Australian Provisional Patent Application No. PO 8560 filed 14 August 1997 (Ex. 2003). Fact ¶ 103. The AU application describes recombinant PAV3 containing a heterologous nucleotide sequence inserted into a non-essential region of the genome. Fact ¶ 74. Incorporation into a non-essential region is critical, because the AU application nowhere discloses helper cell lines that would enable replication of a replication-defective virus. Fact ¶ 75.

Count 1 is directed to a vector created by inserting the heterologous nucleotide sequence into the early region 3 ("E3") of PAV3, which the AU application characterizes (without support) as "non-essential." Fact ¶ 80. The AU application contains virtually

no discussion of the E3 region, much less insertion of foreign DNA into the E3 region. Fact ¶ 79. At its most detailed, the AU application states in relevant part:

> The E3 region of the genome, this also being a non-essential area, has been located and cloned. The promoter region of E3 has been identified and the overlapping L4 area sequenced (Figure 5). The region of the E3 after the polyadenylation signal of the L4 is also a possible site for insertion and can also be used for deletion to create more room for larger cassette insertions.

Fact ¶ 81.[1]

It is clear that this disclosure:

- Does not suggest how an insert into the E3 region could be made; and
- Does not identify where the polyadenylation signal of L4 is located, although it instructs the reader that this is the starting point for insertions.

Fact ¶ 110.

Further, in light of what is now known about PAV3, it is clear that Johnson's suggestion above is impossible to execute. First, there is no "overlapping L4 area" in E3. Fact ¶ 83. The AU application cites a Kleibocker paper (Ex. 2030) demonstrating that the layout of *PAV4* is similar to human adenoviruses in the area of the L4 and E3 regions. Fact ¶ 84. In PAV4, there is an additional polyadenylation site towards the beginning of the E3 region that signals the end of the L4 genes. Fact ¶ 89. In HAV2, L4 overlaps E3. Fact ¶ 85. Therefore Johnson appears to have made the erroneous assumption that E3 in PAV3 would overlap L4 based on his understanding of HAV2 and PAV4. However in PAV3, E3 overlaps with the L5 region, not the L4 region. Fact ¶ 86.

Second, even if one were to assume that the term "L4" in the specification were to be understood to refer to "L5," it would still be impossible to execute Johnson's

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[1] The polyadenylation signal is at the end point of a gene associated with a given region. Fact ¶ 87.

suggestion because in PAV3 the polyadenylation signal of L5 is the same as that of E3. Fact ¶ 90. In other words, the regions are *co-terminal*. Fact ¶¶ 87, 88. Thus, there is nothing left of the E3 region after the polyadenylation site for L5. Fact ¶ 90. The AU application's instructions to use "the region of the E3 after the polyadenylation signal" therefore does not specify any portion of E3 for use as an insertion site. Fact ¶ 91.

These problems are not overcome by Figure 5 of the AU application (Ex. 2003), which purports to be a restriction enzyme map of "PAV3 E3 Sequence." Figure 5 does not, as it purports to do, "illustrate[] the promoter region of E3 and the overlapping L4 area." Fact ¶ 82. The figure reflects that the E3 region is "1618 bps," which is incorrect. Fact ¶¶ 94, 95, 111. E3 is actually only 1179 base pairs long. Fact ¶ 111. The boundaries of E3 are not identified in Figure 5 of the AU Application (and no other showing or reference in the AU application shows the boundaries of E3). Fact ¶¶ 96, 112. Of course, the polyadenylation signal of L4 of PAV3 is not shown, since as discussed above L4 does not in fact overlap with E3. Fact ¶ 110. In sum, it would be impossible to carry out Johnson's suggestion to insert into E3 after the polyadenylation signal of the overlapping L4 region (there is none), or even after the polyadenylation signal of the overlapping L5 region (which is where E3 ends). Fact ¶¶ 97, 114.

D. Legal Standard

In order for a party in an interference to be accorded the benefit of an application, the application must contain a constructive reduction to practice of the subject matter of the Count. 37 C.F.R. § 41.201. A constructive reduction to practice is "a described and enabled anticipation under 35 U.S.C. 102(g)(1) in a patent application of the subject matter of a count." *Id.*

The enablement requirement requires that the specification of an application "teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright*, 999 F.2d 1557, 1561, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). The written description requirement ensures "that, as of the

filing date, the inventor conveyed with reasonable clarity to those of skill in the art that he was in possession of the subject matter" in question. *Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 U.S.P.Q.2d 1227, 1232 (Fed. Cir. 2000). The application "itself must describe an invention, and do so in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997); *see also In re Barker*, 559 F.2d 588, 592 n. 4, 194 U.S.P.Q. 470, 473 n.4 (CCPA 1977) (the goal of the written description requirement is "to clearly convey the information that an applicant has invented the subject matter which is claimed"). The purpose of the written description requirement "is to ensure that the scope of the right to exclude . . . does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345-46, 54 U.S.P.Q.2d 1915, 1917 (Fed. Cir. 2000).

E. The AU Application Does Not Adequately Describe a Recombinant Vector within the Scope of Count 1

Nothing in the AU Application conveys to a person of skill in the art that Johnson invented a recombinant PAV3 stably incorporating homologous DNA into the E3 region. The AU application does not disclose any embodiment of Count 1. Fact ¶¶ 92, 97, 114. Johnson simply calls out the E3 region as "a possible site for insertion." Fact ¶ 81. In order to carry out this suggestion, it would be necessary to have a detailed understanding of the E3 region and its relationship to the other regions of the PAV3 genome. Fact ¶ 45. It is clear from Johnson's multiple mischaracterizations of the E3 gene that Johnson did not have such an understanding. E3 does not overlap with L4 in PAV3, as Johnson says it does. Fact ¶¶ 90-91. Even if a person of skill in the art were to interpret "L4" to refer to L5 in PAV3, it would be impossible to insert in E3 after the polyadenylation signal of L5, because that is where the E3 region ends. Fact ¶ 88.

In addition, the Johnson AU Application is limited to the use of replication-competent PAV3 vectors, and nothing in that application conveys that Johnson had possession of a replication-competent PAV3 incorporating homologous DNA in the E3 region. Fact ¶ 97. For one of ordinary skill to determine whether E3 is non-essential would require confirmatory experiments that are not discussed in the AU application. Fact ¶ 114. The Johnson priority applications do not disclose any helper cell line capable of growing replication-defective PAV3. Fact ¶ 77. Without having had possession of the ability to create either (1) a replication-competent recombinant virus with an insertion within the E3 region, or (2) helper cell lines capable of replicating a disabled virus, Johnson did not possess a "porcine adenovirus" within the scope of Count 1. Fact ¶ 97.

To fulfill the written description requirement of section 112, the application must disclose all of the limitations of the claim, and it must do so in terms such that one skilled in the art can "clearly conclude" that the inventor invented the claimed invention as of the filing date sought. *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966. The disclosure of the AU application fails this test with respect to the recombinant virus of Count 1. Certainly, nothing in the AU application mentions or suggests the 81 to 84 map unit range of Johnson claim 30. Fact ¶ 117.

Even with respect to the alternative Count 1 formulation of Reddy claim 21, all that the disclosure of the AU application shows is that Johnson contemplated that a suitable site for insertion in the E3 region of PAV3 might be found that would not render the virus replication-defective. But far from showing that Johnson had possession of an embodiment of Count 1, the AU application clearly demonstrates that Johnson did *not* yet possess a vector with foreign DNA inserted into E3. Nothing in the disclosure of the AU application describes (1) which portions, if any, of the E3 gene are non-essential or (2) what restriction enzyme might be used to cut the E3 region to make an insertion in a non-essential region. Fact ¶¶ 91,93. Johnson was clearly confused as to the relationship between E3 and late regions L4 and L5 of PAV3, and had no clue where in the E3 region

he could make insertions that would avoid disrupting late region genes – if indeed such an insertion could be made at all.

It is irrelevant whether one of skill in the art might have been able to overcome these problems to create an embodiment of the Count, because the test is not whether what is claimed is "obvious" in light of what is disclosed in the specification. *Lockwood*, 107 F.3d at 1572. Rather the test is whether the disclosure clearly conveys that Johnson was in possession of the claimed invention. *Id.* The best that can be said is that Johnson had a wish or a plan to discover a way to make a recombinant virus within the scope of Count 1. A mere wish or plan for additional research does not fulfill the written description requirement of section 112 paragraph 1. *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 U.S.P.Q.2d 1601, 1606 (Fed. Cir. 1993).

Because it does not describe the PAV3 genome sufficiently to demonstrate Johnson's general ability to manipulate the E3 region of the virus, because it does not describe a working example of a PAV3 stably integrating foreign DNA in the E3 region, and because it suggests only a confused, inoperable plan to try to make such insertions, the AU application (Ex. 2003) does not clearly convey that Johnson had actually or constructively reduced to practice an embodiment of Count 1 as of August 1997.

F. The AU Application (Ex. 2003) Does Not Enable a Scientist of Ordinary Skill To Make a Recombinant Vector within the Scope of Count 1.

Because, as discussed above, significant experimentation would be required before a person of skill in the art could practice the invention of Count 1, the AU application fails to enable one of skill in the art to practice the invention. First, it is impossible to follow Johnson's suggestion to insert into the E3 region after the polyadenylation signal of the overlapping L4 region, because it is the L5 region, not the L4 region, that overlaps E3 in PAV3, and there is no portion of E3 after the polyadenylation signal of L5. Fact ¶¶ 88, 90, 91. Second, even if one selected an insertion point within the E3 region, the specification does not provide any guidance to

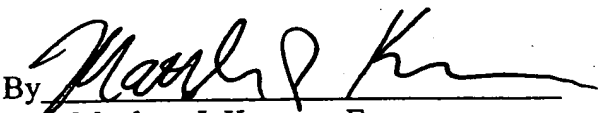
the reader to avoid inserting in essential late regions that overlap the E3 region. Fact ¶ 114. And finally, even if one were to overcome both of these hurdles, one could still not expect, based on the teaching of the AU application and the state of the art at the time of filing, that the resulting recombinant antibody would be replication competent, since there was no evidence in the art at the time or in the AU application (beyond Johnson's unsupported assertion), that the PAV3 E3 region is not essential to viral replication. Fact ¶ 80. Indeed, as late as 2004, Johnson submitted evidence to the examiner of the '512 application (Ex. 2002) that suggests that nearly all of the E3 region overlaps with the late L5 region that encodes the essential pVIII protein. Fact ¶ 86. Thus, Johnson does not enable any embodiment within the scope of count 1.

III. CONCLUSION

The AU application (Ex. 2003) does not describe a recombinant vector claimed in Johnson claim 30 and Reddy claim 21, nor does it enable a scientist of ordinary skill to make and use the recombinant vector of those claims. Thus, Reddy respectfully requests that the Board grant this motion and deny Johnson the benefit of the AU application.

Dated: February 24, 2006

Respectfully submitted,

By 

Matthew I. Kreeger, Esq.
Registration No.: 56,398
Lead Attorney for Junior Party Reddy

MORRISON & FOERSTER LLP
425 Market Street
San Francisco, CA 94105
Tel: (415) 268-7000
Fax: (415) 268-7522
Email: mkreeger@mofo.com

APPENDIX A (EVIDENCE IN SUPPORT OF THE MOTION)

In support of this motion, Reddy relies on Reddy Exhibit Nos. 2001-2007, 2009, 2013-2036:

1. Reddy U.S. Patent No. 6,492,343, filed April 14, 1999 (Ex. 2001).
2. Johnson U.S. Patent Application No. 09/485,512, filed May 5, 2000 (Ex. 2002).
3. Johnson Australian Provisional Patent Application No. PO 8560, filed August 14, 1997 (Ex. 2003).
4. Johnson International Patent Application No. PCT/AU98/00648, filed August 14, 1998 (Ex. 2004).
5. Paper No. 1 in Patent Interference No. 105,358 mailed October 19, 2005 (Declaration of Interference under Bd.R. 203(d)) (Ex. 2005).
6. Paper No. 24 in Patent Interference No. 105,358 mailed January 24, 2006 (Redeclaration of Interference under Bd.R. 203(d)) (Ex. 2006).
7. Reddy U.S. Provisional Patent Application No. 60/081,882 filed April 15, 1998 (Ex. 2007).
8. Declaration of Katherine J. Spindler, Ph.D. ("Spindler Decl.") dated February 22, 2005. (Ex. 2009).
9. Johnson Clean Copy of Claims, 9 pages (Ex. 2013).
10. Thomas Shenk, Ch. 67: *Adenoviridae: The Viruses and Their Replication.* FIELDS VIROLOGY, 2111-2148 (3rd ed., B.N. Fields et al. eds. Lippincott – Raven Publishers, Philadelphia, 1996) (Ex. 2014).
11. Jean-Luc Imler et al., *Trans-Complementation of E1-Deleted Adenovirus: A New Vector To Reduce The Possibility Of Codissemination Of Wild-Type And*

Recombinant Adenoviruses. HUMAN GENE THERAPY 6, 711-721 (1995). (Ex. 2015).

12. Marshall S. Horwitz, Ch. 68: *Adenoviruses,* FIELDS VIROLOGY B. N. Fields B.N. et al. eds. Lippincott – Raven Publishers, Philadelphia, 2149-71 (1996) (Ex. 2016).

13. F. L. Graham, F. L., et al., *Characteristics Of A Human Cell Line Transformed By DNA From Human Adenovirus Type 5,* JOURNAL OF GENERAL VIROLOGY 36, 59-72 (1977) (Ex. 2017).

14. J. B. Derbyshire, et al. *Serological And Pathogenicity Studies With Some Unclassified Porcine Adenoviruses,* JOURNAL OF COMPARATIVE PATHOLOGY 85, 437-443 (1975) (Ex. 2018).

15. Tadashi Hirahara et al., *Isolation Of Porcine Adenovirus From The Respiratory Tract Of Pigs In Japan,* JAPANESE JOURNAL OF VETERINARY SCIENCES 52: 407-409 (1990)) (Ex. 2019).

16. T. Tuboly et al., *Potential Viral Vectors For The Stimulation Of Mucosal Antibody Responses Against Enteric Viral Antigens In Pigs,* RESEARCH IN VETERINARY SCIENCE 54, 345-350 (1993). (Ex. 2020).

17. P. Seshidhar Reddy, et al., *Restriction Endonuclease Analysis and Molecular Cloning of Porcine Adenovirus Type 3*. INTERVIROLOGY 36, 161-168 (1993) (Ex. 2021).

18. P. Seshidhar Reddy et al., *Sequence Analysis of Putative pVIII, E3 and Fibre Regions of Porcine Adenovirus Type 3*, VIRUS RESEARCH 36, 97-106 (1995) (Ex. 2022).

19. P. Seshidhar Reddy et al., *Comparison of Inverted Terminal Repetition Sequences From Five Porcine Adenovirus Serotypes,* VIROLOGY 212, 237-239 (1995) (Ex. 2023).

20. P. Seshidhar Reddy et al., *Porcine Adenovirus Types 1, 2 And 3 Have Short And Simple Early E-3 Regions.* VIRUS RESEARCH 43, 99-109 (1996) (Ex. 2024).

21. P. Seshidhar Reddy et al., *Characterization of the early region 4 of porcine adenovirus type 3*, VIRUS GENES 15, 87-90 (1997) (Ex. 2025).

22. R. J. McCoy, et al., *Genomic Location And Nucleotide Sequence of A Porcine Adenovirus Penton Base Gene,* ARCHIVES OF VIROLOGY 141, 1367-1375 (1996) (Ex. 2026).

23. R. J. McCoy et al., *Nucleotide And Amino Acid Sequence Analysis Of The Porcine Adenovirus 23K Protein,* DNA SEQUENCE 6, 251-254 (1996) (Ex. 2027).

24. R. J. McCoy et al. *Nucleotide and Amino Acid Sequence Analysis of the 100K Protein of a Serotype 3 Porcine Adenovirus,* DNA SEQUENCE 8, 59-61 (1997) (Ex. 2028).

25. P. Seshidhar Reddy et al., *Nucleotide Sequence And Transcription Map Of Porcine Adenovirus Type 3,* VIROLOGY 251(2):414-426 (1998) (Ex. 2029).

26. Steven B. Kleiboeker, *Sequence Analysis of Putative E3, pVIII, and Fiber Genomic Regions of a Porcine Adenovirus,* VIRUS RESEARCH, 31:17-25 (1994). (Ex. 2030).

27. Prosecution history of the '512 patent application,first declaration of Dr. Jeffrey Michael Hammond Under 37 C.F.R. §1.132, 19 pages total, with Response to Office Action mailed on April 1, 2003, 14 pages. (Ex. 2031).

28. Prosecution history of the '512 patent application, response to final Office Action filed with the U.S. Patent and Trademark Office on August 13, 2004, 9 pages. (Ex. 2032).

29. Prosecution history of the '512 patent application, Second Declaration of Dr. Jeffrey Michael Hammond Under 37 C.F.R. §1.132, 7 pages, with Response to Office Action mailed on February 27, 2004, 19 pages. (Ex. 2033).

30. Amended PCT Patent Application No. PCT/AU98/00648 filed November 11, 1999 (Ex. 2034).

31. Andrew J. Bett et al., *Packaging Capacity and Stability of Human Adenovirus Type 5 Vectors* JOURNAL OF VIROLOGY 67(10) 5911-5921 (1993) (Ex. 2035).

32. P. Seshidhar Reddy et al., *Development of Porcine Adenovirus-3 as an Expression Vector,* JOURNAL OF GENERAL VIROLOGY 80, 563-570 (1999) (Ex. 2036).

APPENDIX B (STATEMENT OF MATERIAL FACTS)

A. Adenoviruses

1. Adenoviruses are DNA viruses that infect the respiratory tract, intestines, and other mucous membranes of a large variety of animals and birds. Known adenoviruses include human ("HAV"), porcine ("PAV"), bovine ("BAV"), mouse ("MAV"), and many others. (Ex. 2009 Spindler Decl. at ¶ 10 (*citing* Ex. 2014)).

2. Multiple strains, or "serotypes," of each of these types of adenoviruses are known to exist. These are referred to by number. (Ex. 2014; Ex. 2009 Spindler Decl. at ¶ 10 (*citing* Ex. 2014)).

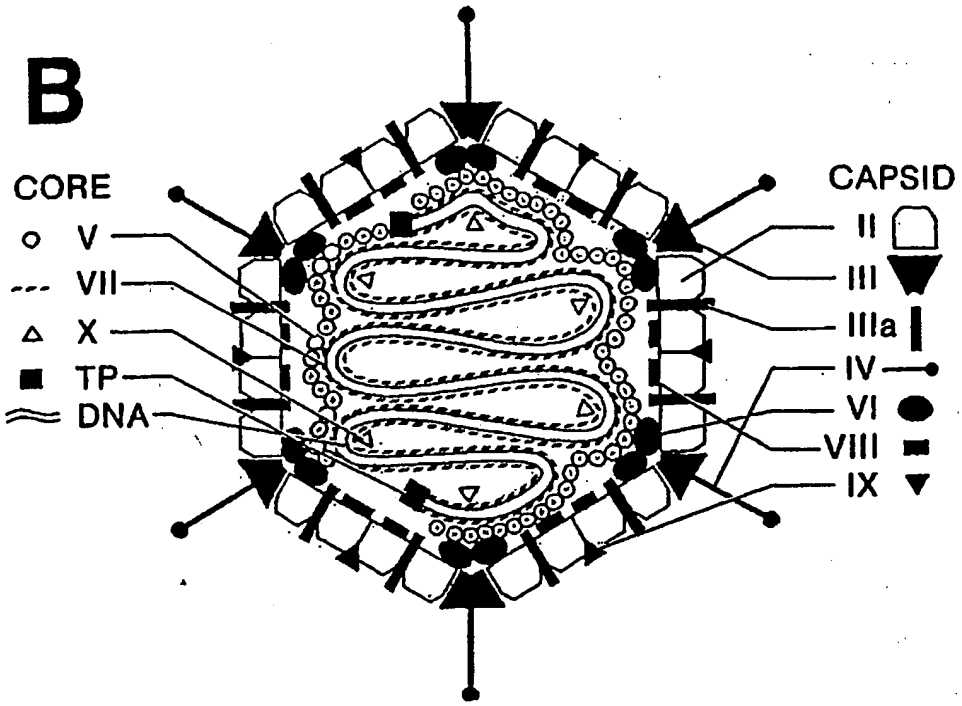
3. Human adenovirus serotype 2 is referred to as HAV2. (Ex. 2009 Spindler Decl. at ¶ 10 (*citing* Ex. 2014)).

4. As of August 1997, certain adenoviruses were well characterized in the art. (Ex. 2009 Spindler Decl. at ¶ 10 (*citing* Ex. 2014)).

5. Since 1987, researchers have studied the potential use of adenoviruses as vectors for the delivery and expression of foreign DNA. (Ex. 2009 Spindler Decl. at ¶ 11 (*citing* Ex. 2015, Ex. 2016 at page 2165)).

6. Certain adenoviruses are known to be relatively harmless to the infected immunocompetent human or animal, but highly effective in stimulating an immune response. Scientists realized that a benign adenovirus might be recombined with DNA encoding antigens of more virulent pathogens in order to create a vaccine. (Ex. 2009 Spindler Decl. at ¶ 12 (*citing* Ex. 2020)).

7. Adenoviruses have icosahedral capsids that are composed of proteins, as is shown in the representation of the structure of human adenovirus serotype 2 ("HAV2") below:



(Ex. 2009 Spindler Decl. at ¶ 13 (*citing* Ex. 2014, Shenk et al., at page 2115, Figure 2B)).

8. Capsid proteins are critical structural elements that the virus requires to survive. (Ex. 2009 Spindler Decl. at ¶ 14 (*citing* Ex. 2014, at page 2116, Figure 3)).

9. The proteins that comprise the adenovirus are identified by Roman numerals. Thus, for example, pVIII refers to capsid protein numeral VIII. (Ex. 2009 Spindler Decl. at ¶ 14 (*citing* Ex. 2014, at page 2116, Figure 3)).

10. The major capsid proteins are also know by other names such "fiber" for pIV, "hexon" for pII, and "penton" for pIII. (Ex. 2009 Spindler Decl. at ¶ 14 (*citing* Ex. 2014, at page 2116, Figure 3)).

11. The adenovirus genome consists of a single linear, double-stranded DNA. (Ex. 2009 Spindler Decl. at ¶ 15 (*citing* Ex. 2014, at page 2115, paragraph bridging left and right columns)).

12. Transcription of adenovirus DNA is accomplished in two phases: the early phase and the late phase. (Ex. 2009 Spindler Decl. at ¶ 15).

13. During the early phase, the virus selectively transcribes certain "early genes" that perform a variety of functions to create the necessary pre-conditions for viral replication. (Ex. 2009 Spindler Decl. at ¶ 15).

14. Early genes are identified by number E1 through E4. (Ex. 2009 Spindler Decl. at ¶ 15).

15. Once early phase transcription is complete, transcription of the "late genes" may begin. (Ex. 2009 Spindler Decl. at ¶ 16).

16. The products of late genes include the capsid proteins. (Ex. 2009 Spindler Decl. at ¶ 16).

17. Viral DNA is transcribed in blocks known as transcription units, which can be processed into multiple mRNAs. (Ex. 2009 Spindler Decl. at ¶ 17).

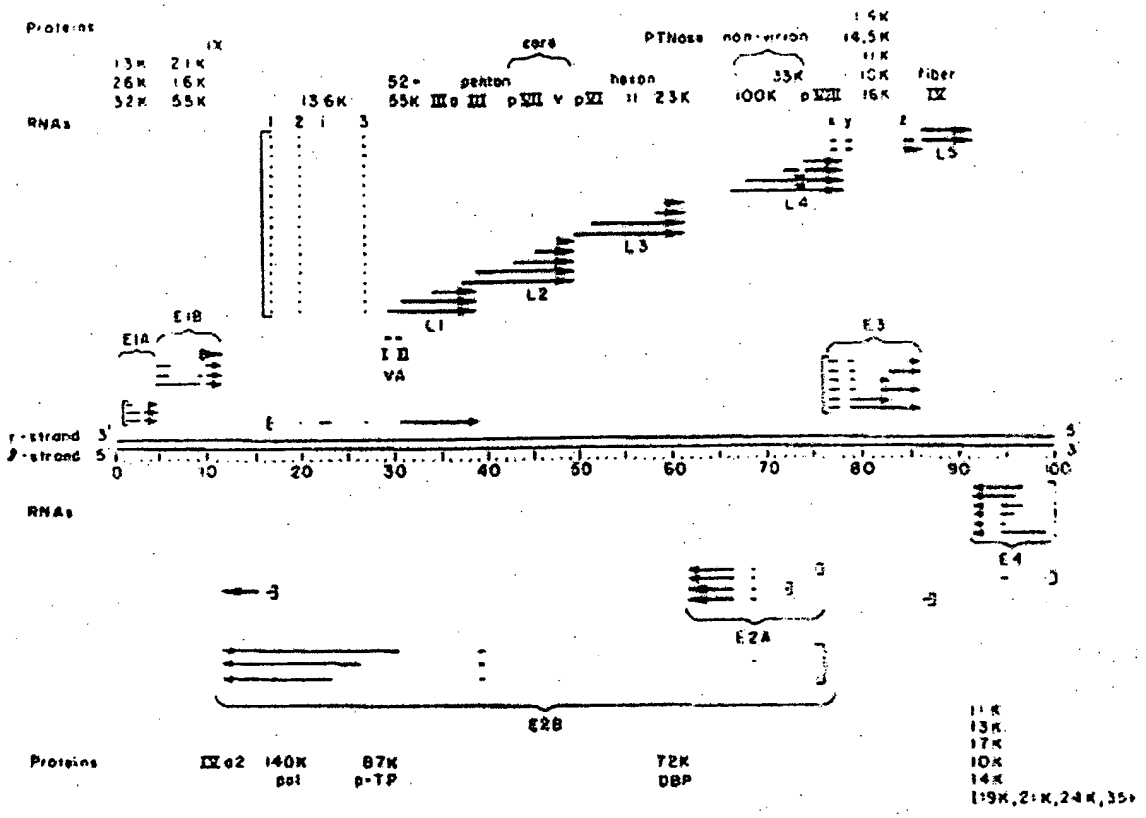
18. A single mRNA may consist of one or more "open reading frame" each of which can be translated into a protein. (Ex. 2009 Spindler Decl. at ¶ 17).

19. The open reading frame for one gene or protein may overlap with the open reading frame for another. (Ex. 2009 Spindler Decl. at ¶ 17).

20. As a result of overlapping open reading frames in a virus genomic sequence, the same sequence of nucleotides may be part of more than one gene. (Ex. 2009 Spindler Decl. at ¶ 17).

21. The arrangement of "open reading frames" or genes on a viral genome is commonly illustrated in a "genome map." (Ex. 2009 Spindler Decl. at ¶ 17)

22. Reproduced below is the genome map of the human adenovirus serotype 2 (HAV2), as it was understood before August 1997. (Ex. 2009 Spindler Decl. at ¶ 17 (*citing* Ex. 2014, at page 2116, Figure 3)).



23. The genome map reproduced above employs the convention of "map units." (Ex. 2009 Spindler Decl. at ¶ 18).

24. A "map unit" is a conventional tool in the art for referring to portions of a genome. A genome is "mapped" by dividing the whole genome into 100 units. (Ex. 2009 Spindler Decl. at ¶ 18).

25. The specific point to which a given map unit (for example, 81) refers depends on the size of the genome. Map unit 81 refers to the 810th base in a genome of 1000 base, and to the 4,050th base in a genome of 5000 bases, for example. (Ex. 2009 Spindler Decl. at ¶ 18).

26. HAV2 has five early regions (numbered E1A, E1B, E2 (E2A and E2B), E3, and E4) and five late regions (numbered L1 through L5). (Ex. 2009 Spindler Decl. at ¶ 19 (*citing* Ex. 2014, at page 2115, right column, first full paragraph)).

27. In a genome map, each mRNA within each region is represented by an arrow. The body of the arrow represents the nucleotides that are transcribed to produce the mRNA. The direction of the arrow represents the direction of transcription. (Ex. 2009 Spindler Decl. at ¶ 19).

28. A given nucleotide sequence may be transcribed into a primary transcript that is processed in multiple ways to produce several different mRNAs within a given region. (Ex. 2009 Spindler Decl. at ¶ 19).

29. Early and late regions may overlap. For example, as shown above, in HAV2, the L4 region and the E3 region overlap. Thus, in HAV2 the same sequence of nucleotides will be involved in expressing both the early region genes of E3 and the late region genes of L4. (Ex. 2009 Spindler Decl. at ¶ 19).

30. The number and arrangement of early and late regions vary among adenovirus types and serotypes. (Ex. 2009 Spindler Decl. at ¶ 19).

31. The late regions of HAV2 encode structural proteins such as pVIII, which are essential for production of viral particles. (Ex. 2009 Spindler Decl. at ¶ 20 (*citing* Ex. 2014, at Figures 2B and 3, and 2113-2116)).

32. The early genes generally encode proteins responsible for replication and transcription of the viral genome, and interactions with the host cell and host immune response. (Ex. 2009 Spindler Decl. at ¶ 21 (*citing* Ex. 2014, at Figure 5 and at pages 2119-2129)).

33. In HAV2, the E3 gene encodes proteins that modulate response of the host cells to adenovirus infection. (Ex. 2009 Spindler Decl. at ¶ 21 (*citing* Ex. 2014, at page 2117, left column, lines 18-20)).

34. In some circumstances, the products of some early region genes may not be needed for efficient viral growth in cultured cells. (Ex. 2009 Spindler Decl. at ¶ 21 (*citing* Ex. 2014, at page 2134, sentence bridging left and right columns)).

35. Scientists have experimented with recombinant techniques to insert foreign DNA into adenoviruses in such a way that the adenovirus retains the ability to replicate because the expression of one or more of the adenovirus's genes may be disrupted depending on where in the genome the foreign genes are inserted. (Ex. 2009 Spindler Decl. at ¶¶ 22, 24).

36. In some cases, the genes that are disrupted may be essential to the formation of the adenovirus rendering the resulting vector replication-defective. (Ex. 2009 Spindler Decl. at ¶ 22).

37. In such cases, the adenovirus recombinant cannot form except in the presence of a "helper" cell that is designed to supply the missing protein or proteins that are associated with the disabled gene or genes. (Ex. 2009 Spindler Decl. at ¶ 22 (*citing* Ex. 2016 at page 2165-2166)).

38. Human adenoviral vectors with insertions in the essential region E1 are produced in complementing cell lines such as the human embryonic kidney "293" cell line, which expresses E1 proteins. (Ex. 2009 Spindler Decl. at ¶ 23 (*citing* Ex. 2017, and Ex. 2016, at page 2166, right column)).

39. The Reddy patent-in-interference (the '343 patent) discloses "helper-dependent" recombinant adenovirus vectors grown in helper cell lines. (Ex. 2001 the '343 patent, col. 22 line 46 – col. 23, line 16).

40. By experimentation it is sometimes possible to identify certain areas of the adenovirus genome that are not essential to viral replication. (Ex. 2009 Spindler Decl. at ¶ 24).

41. When insertions of foreign DNA are made in non-essential regions, the result may be a "helper-independent" recombinant adenovirus. (Ex. 2009 Spindler Decl. at ¶ 24).

42. In HAV2, the E3 region of human adenovirus was found to be non-essential for growth in tissue culture. Accordingly, it is possible to create a helper-

independent virus by making insertions of foreign DNA in the E3 region of HAV2. (Ex. 2009 Spindler Decl. at ¶ 24 (*citing* Ex. 2016, at 2165, right column)).

43. A given nucleotide sequence may be involved in the expression of multiple genes, some of which may be essential to viral replication, and some of which may be non-essential. (Ex. 2009 Spindler Decl. at ¶ 25).

44. Types and serotypes of adenoviruses vary significantly from one another in terms of the number of genes, their location in the genome, and the extent to which the proteins that they encode are necessary for viral replication. (Ex. 2009 Spindler Decl. at ¶ 25).

45. It is necessary to have precise knowledge of the genome of the particular type and serotype of adenovirus under investigation in order to predict which genes may be disrupted by insertions of foreign genes in a given location, or to predict which insertions are likely to render the virus replication-defective. (Ex. 2009 Spindler Decl. at ¶ 25).

46. Adenoviruses have a limit to the amount of DNA that they can encapsidate. (Ex. 2009 Spindler Decl. at ¶ 26 (*citing* Ex. 2035)).

47. In order to make room for foreign genes, it is sometimes useful to delete portions of the native adenovirus DNA. (Ex. 2009 Spindler Decl. at ¶ 26).

48. Deletions of native adenovirus DNA may prevent the expression of any genes that are associated with the deleted nucleotides. (Ex. 2009 Spindler Decl. at ¶ 26).

49. If so, then the resulting adenovirus will not assemble into an infectious recombinant adenovirus particle except in a suitable complementary helper cell line. (Ex. 2009 Spindler Decl. at ¶ 26).

B. Porcine Adenovirus 3

50. At least five different serotypes of porcine adenoviruses ("PAV") were known to exist in 1995, although none had been fully characterized. (Ex. 2009 Spindler Decl. at ¶ 27 (*citing* Exs. 2018 and 2019)).

51. Porcine adenoviruses have minimal pathogenicity. (Ex. 2009 Spindler Decl. at ¶ 28).

52. At least by 1993 they had been proposed as vectors for viral vaccines. (Ex. 2009 Spindler Decl. at ¶ 28 (*citing* Ex. 2020, at pages 345-350)).

53. In particular, the serotype PAV3 was thought to be a suitable vector based on its low virulence and the ability to grow well in cell culture. (Ex. 2009 Spindler Decl. at ¶ 28 (*citing* Ex. 2020 at pages 345-350)).

54. Compared to its human adenovirus counterparts, relatively little was known about PAV3 as of August 1997. (Ex. 2009 Spindler Decl. at ¶ 29).

55. By August 1997, Reddy had isolated the PAV3 genome, determined its restriction map and cloned fragments representing the entire genome. (Ex. 2009 Spindler Decl. at ¶ 29 (*citing* Ex. 2021 at page 162, 1st ¶, last sentence)).

56. Reddy had also prepared a map showing generally where enzyme cleavage sites occur within the genome. (Ex. 2009 Spindler Decl. at ¶ 29 (*citing* Ex. 2021 at page 166, Figure 4)).

57. As of August 1997, the region encoding pVIII, E3 and fibre regions of PAV3 were sequenced by 1995 by Reddy and others. (Ex. 2009 Spindler Decl. at ¶ 30 (*citing* Ex. 2022)).

58. As of August 1997, the inverted terminal repeat (ITR) sequences flanking PAV genomes were also sequenced by 1995 by Reddy and others. (Ex. 2009 Spindler Decl. at ¶ 30 (*citing* Ex. 2023)).

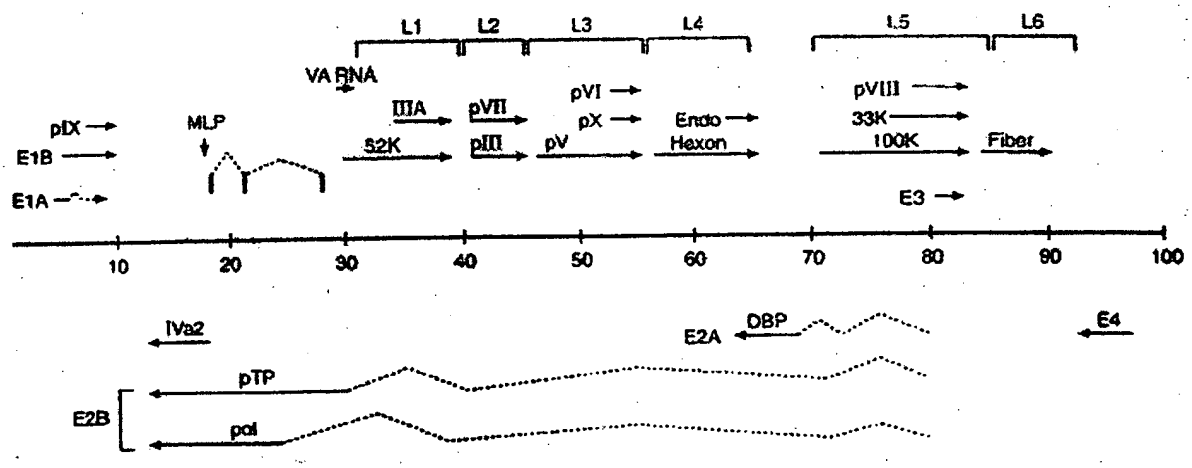
59. As of August 1997, a comparison of the E3 regions of PAVs-1, 2 and 3 had been published in 1996 by Reddy and others. (Ex. 2009 Spindler Decl. at ¶ 30 (*citing* Ex. 2024)).

60. As of August 1997, the E4 region of E3 had been sequenced and 5' and 3' ends of transcripts characterized by 1997 by Reddy and others. (Ex. 2009 Spindler Decl. at ¶ 30 (*citing* Ex. 2025)).

61. As of August 1997, the sequences of the late PAV3 gene encoding the structural proteins penton and 23K were published in 1996. (Ex. 2009 Spindler Decl. at ¶ 30 (*citing* Exs. 2026 and 2027)).

62. The sequence of the late PAV3 gene encoding the structural protein, 100K was published in 1997. (Ex. 2009 Spindler Decl. at ¶ 30 (*citing* Ex. 2028)).

63. In 1998 Reddy published the genome map of PAV3 shown below (Ex. 2009 Spindler Decl. at ¶ 31 (*citing* Ex. 2029, at page 420, Figure 1)).



The arrows represent genes or groups of genes that are transcribed in PAV3. Above the map unit line are genes that are transcribed left-to-right, and below the line are genes that are transcribed right-to-left.

64. As of August 1997, the full sequence of PAV3 was not known. (Ex. 2009 Spindler Decl. at ¶ 32).

65. As of August 1997, there was no published PAV3 genome map of the kind shown above available to show how the various regions and genes of the genome are arranged. (Ex. 2009 Spindler Decl. at ¶ 32).

66. As of August 1997, the exact size of the PAV3 genome was not known. (Ex. 2009 Spindler Decl. at ¶ 32).

67. Researchers in the field sometimes relied on their understanding of well-known adenovirus types and serotypes for clues about the structure of PAV3. (Ex. 2009 Spindler Decl. at ¶ 33).

68. The overall genome organization of PAV3 is similar, but not identical, to HAV2. (Ex. 2009 Spindler Decl. at ¶ 33).

69. Such a comparison between PAV3 and HAV2 is not reliable for making specific predictions about the structure of PAV3 because homology among types of adenovirus, or even among serotypes (e.g. PAV3 and PAV4) is not strong. (Ex. 2009 Spindler Decl. at ¶ 34 (Ex. 2022, at pages 104-105; Ex. 2024, at paragraph bridging pages 107-108)).

70. Distinctive features of the PAV3 genome not found in HAV-2 include the organization of late region genes into six families instead of five, the absence of additional leader sequences in transcripts of the fibre gene, and the presence of a single small virus-associated RNA gene. (Ex. 2009 Spindler Decl. at ¶ 34 (*citing* Ex. 2029, right column, at lines 8-15)).

71. The nucleotide sequence and transcription map of the entire PAV3 genome was first published in 1998 by Reddy and others and revealed that the PAV3 genome is 34,094 base pairs long. (Ex. 2009 Spindler Decl. at ¶ 35 (*citing* Ex. 2029)).

72. The '343 patent includes a disclosure of the sequence and transcription map of the entire PAV3 genome. (Figure 1 (sequence) and Figure 2 (transcription map) of the '343 patent.) (Ex. 2009 Spindler Decl. at ¶ 35 (*citing* Ex. 2001)).

C. **No Embodiment of the Invention of Count 1 is Described or Enabled by the Disclosures of the AU Application (Ex. 2003).**

73. The AU Application discloses only helper-independent recombinant PAV3. (Ex. 2009 Spindler Decl. at ¶¶ 43-44 (*citing* Ex. 2003)).

74. Johnson's AU application discloses a recombinant PAV3 incorporating foreign genes into non-essential regions of the genome for the purpose of creating helper-independent viral vectors. (Ex. 2009 Spindler Decl. at ¶ 43 (*citing* Ex. 2003)).

75. The AU application discusses insertion only into non-essential regions. ("The DNA of interest which may comprise heterologous genes coding for antigenic determinants or immuno-potentiator molecules may be located in at least one non-essential region of the viral genome."). (Ex. 2009 Spindler Decl. at ¶ 44 (*citing* Ex. 2003, page 6, lines 13-15)).

76. The AU application does not discuss insertion of foreign sequences into essential regions of the genome. (Ex. 2009 Spindler Decl. at ¶ 44 (*citing* Ex. 2003)).

77. The AU application does not disclose helper cell lines capable of replicating helper-dependent viruses. (Ex. 2009 Spindler Decl. at ¶ 44 (*citing* Ex. 2003)).

78. A person of ordinary skill in the field of adenoviruses in 1997 could not have created helper-dependent viruses and complementing cell lines based on the teachings of the AU application without extensive experimentation. (Ex. 2009 Spindler Decl. at ¶ 45 (*citing* Ex. 2003)).

79. The AU application does not describe inserting foreign genes into the E3 region. (Ex. 2009 Spindler Decl. at ¶¶ 47-52 (*citing* Ex. 2003)).

80. The AU application characterizes the E3 region of PAV-3 (without support) as "non-essential." (Ex. 2009 Spindler Decl. at ¶¶ 46 and 47 (*citing* Ex. 2003)).

81. The AU Application suggests that E3 might be suitable for insertion "after the polyadenylation signal" of the "overlapping L4" region. ("The E3 region of the genome, this also being a non-essential area, has been located and cloned. The promoter

region of E3 has been identified and the overlapping L4 area sequenced (Figure 5). The region of the E3 after the polyadenylation signal of the L4 is also a possible site for insertion and can also be used for deletion to create more room for larger cassette insertions."). (Ex. 2009 Spindler Decl. at ¶ 47 (*citing* Ex. 2003, page 14, lines 4-9)).

82. Similarly, at page 11 lines 2-3 of the AU application, the Figure 5 sequence is purported to show "the promoter region of E3 and the overlapping L4 area." Neither are identified in Figure 5. (Ex. 2009 Spindler Decl. at ¶ 47 (*citing* Ex. 2003, page 11 lines 2-3)).

83. In PAV3, the E3 region does not overlap with L4. (Ex. 2009 Spindler Decl. at ¶ 48).

84. The AU application cites a Kleiboecker 1994 (Ex. 2030) paper demonstrating that the layout of PAV4 was similar to human adenoviruses in the area of the L4 and E3 regions (Ex. 2009 Spindler Decl. at ¶ 48 (*citing* Ex. 2003 at page 4 lines 25-29; Figure 2)).

85. In HAV2, L4 overlaps E3. (Ex. 2009 Spindler Decl. at ¶ 48).

86. In PAV3, E3 overlaps with the L5 region. (Ex. 2009 Spindler Decl. at ¶ 48 (*citing* Ex. 2029, at page 420, Figure 1 reproduced above at paragraph 63; *see also* Ex. 2033, Exhibit A submitted with Rule 132 declaration of J. Hammond, Feb. 26, 2004, submitted by Johnson during prosecution of the '512 application).

87. The end of a messenger RNA is formed 10 to 30 nucleotides downstream of the polyadenylation signal, which is a specific nucleotide sequence (AAUAAA). Thus, the polyadenylation signal is found 10-30 nucleotides upstream from the end point of the genes associated with a given region. As a result, genes that share a common polyadenylation signal are co-terminal. (Ex. 2009 Spindler Decl. at ¶ 49).

88. In PAV3 (unlike HAV2), the E3 region and the L5 region share the same polyadenylation site and are therefore co-terminal. (Ex. 2009 Spindler Decl. at ¶ 49

(*citing* Ex. 2022, at Figures 1 and 2, and page 100; Ex. 2024, at page 106 and Figure 7; Ex. 2029, at Table 2; and Ex. 2036, at page 569)).

89. In PAV4, there is an additional polyadenylation site towards the beginning of the E3 region that signals the 3' end of the L4 gene. (Ex. 2009 Spindler Decl. at ¶ 49).

90. Even if one were to assume that the term "L4" in the specification were to be construed as "L5," it would still be impossible to execute Johnson's suggestion because in PAV3 the polyadenylation signal of L5 is the same as that of E3 – none of the E3 region is after the polyadenylation site for L5. (Ex. 2009 Spindler Decl. at ¶ 49).

91. The AU application's instructions to use "the region of the E3 after the polyadenylation signal" does not specify any portion of E3 for use as an insertion site. (Ex. 2009 Spindler Decl. at ¶ 49 (*citing* Ex. 2003 at page 14, lines 6-7)).

92. Nothing else in the AU application describes the insertion of foreign DNA into the E3 region of PAV3. (Ex. 2009 Spindler Decl. at ¶ 51 (*citing* Ex. 2003)).

93. No example of a recombinant virus constructed by insertion of foreign DNA into the E3 region is given that would demonstrate the non-essential region of E3. (Ex. 2009 Spindler Decl. at ¶ 51 (*citing* Ex. 2003)).

94. Figure 5 of the AU application illustrates the organization and restriction map of a 1618 bp fragment labeled "PAV3 E3 sequence." (Ex. 2009 Spindler Decl. at ¶ 51 (*citing* Ex. 2003, Figure 5, page 11 lines 2-3)).

95. Figure 5 is not limited to E3, because E3 is significantly smaller than 1618 bp. (Ex. 2009 Spindler Decl. at ¶ 51 (*citing* Ex. 2003, Figure 5; Ex. 2022 at page 97)).

96. Figure 5 also does not identify where E3 begins and ends in relation to the three overlapping segments, and it does not show any gene sequences. (Ex. 2009 Spindler Decl. at ¶ 51 (*citing* Ex. 2003)).

97. The AU application does not indicate that Johnson possessed a recombinant PAV3 vector incorporating foreign DNA into the E3 region of the genome,

much less in the specific 81-84 map unit portion of E3. (Ex. 2009 Spindler Decl. at ¶ 52 (*citing* Ex. 2003)).

D. Count 1 of the Interference

98. Count 1 of the interference is Claim 30 of the 09/485,512 application ("the '512 application" Ex. 2002) or Claim 21 of Reddy United States Patent No. 6,492,343 ("the '343 patent" Ex. 2001). (Ex. 2005 Declaration of Interference mailed October 19, 2005).

99. Claim 30 of the '512 application ("Johnson Claim 30"), which depends from claim 2, corresponds to:

> A recombinant vector including a recombinant porcine adenovirus stably incorporating, and expressing heterologous DNA wherein said heterologous DNA is stably integrated into the adenovirus E3 region of the genome at map units from about 81 to about 84 of PAV3

(Ex. 2009 Spindler Decl. at ¶ 6 (*citing* Ex. 2005 Declaration of Interference mailed October 19, 2005; Ex. 2013 Johnson clean copy of claims in the '512 application)).

100. Claim 21 of the '343 patent ("Reddy Claim 21") corresponds to:

> A recombinant PAV-3 vector comprising a PAV-3 genome capable of duplex formation under conditions of high stringency to the PAV-3 genome as depicted in SEQ ID NO:1, or a complement thereof and at least one heterologous nucleotide sequence, wherein the heterologous nucleotide sequence is inserted in the E3 region.

(Ex. 2009 Spindler Decl. at ¶ 6 (*citing* Ex. 2005 Declaration of Interference mailed October 19, 2005; and '343 patent, Ex. 2001)).

101. The Notice Declaring Interference (37 C.F.R. § 41.203(d)) (Ex. 2005) accorded Johnson 35 U.S.C. § 102(g) benefit from Johnson PCT patent application No. PCT/AU98/00648, filed August 14, 1998; and Australian application No. PO 8560, filed August 14, 1997. (respectively Ex. 2004 and Ex. 2003.)

102. All of Johnson's claims in interference contain limitations directed towards insertions of heterologous DNA within certain map unit ranges. (Ex. 2005 Declaration of Interference mailed October 19, 2005).

E. The Disclosures in the AU application.

103. The earliest priority document to which Johnson has been accorded benefit is Australian application No. PO 8560 filed 14 August 1997. (Ex. 2005, Declaration, Paper No. 1, at 4.)

104. The AU application relates to a recombinant PAV3 containing a heterologous nucleotide sequence inserted into a non-essential region of the genome. (Ex. 2009 Spindler Decl. at ¶ 44 (*citing* Ex. 2003)).

105. Incorporation into a non-essential region is critical because the AU application nowhere discloses helper cell lines that would enable replication of a replication-defective vector. (Ex. 2009 Spindler Decl. at ¶ 44 (*citing* Ex. 2003)).

106. Count 1 is directed to a vector created by inserting the heterologous nucleotide sequence into the early region 3 ("E3") of PAV3. (Ex. 2005 Declaration of Interference mailed October 19, 2005).

107. Johnson claim 30, which is one of the alternative formulations of Count 1, specifies that the insertion is to be made at map units from about 81 to about 84 of PAV3. (Ex. 2009 Spindler Decl. at ¶ 6 (*citing* Ex. 2005 Declaration of Interference mailed October 19, 2005)).

108. The AU application suggests a portion of E3 as a possible insertion site, but does not show that Johnson had actually made an insertion at that point and achieved stable integration of homologous nucleotides.[2] No supporting reference is cited. (Ex. 2009 Spindler Decl. at ¶ 47 (*citing* AU application, Ex. 2003, at page 14, lines 4-8)).

[2] This description is also erroneous in that E3 does not overlap the L4 gene in PAV3. This was an assumption that Johnson apparently made by analogy to PAV-4 and

109. The suggestion to insert in the E3 region was already known in the art. (Ex. 2022 Reddy et al (1995); Ex. 2024 Reddy et al (1996)).

110. The polyadenylation signal of L4, which according to the AU application marks the beginning point for possible insertions into E3, is nowhere identified in the AU application (Ex. 2003).

111. Figure 5 of the AU application states that the E3 region is "1618 bps," which is incorrect. E3 is actually 1179 base pairs long. (Ex. 2009 Spindler Decl. at ¶ 51 (*citing* Ex. 2003, Figure 5 and Ex. 2022 at page 97)).

112. The AU application does not disclose the boundaries of E3. (Ex. 2009 Spindler Decl. at ¶ 51 (*citing* Ex. 2003, Figure 5; Ex. 2022 at page 97)).

113. No gene sequence or transcription map is provided for PAV3 or the E3 region of PAV-3 is shown in the AU application. (Ex. 2003).

114. The AU patent application does not provide one of ordinary skill with adequate guidance of the metes and bounds of where in E3 insertions can be made. Without undue experimentation, one of ordinary skill will not know which region within E3 is suitable for insertion. (Ex. 2009 Spindler Decl. at ¶¶ 51-52 (*citing* Ex. 2003)).

115. Human and animal adenoviruses were known by one of ordinary skill in the art to be different. The AU patent application acknowledges that Kleibocker (1994) that although PAV4 has similar arrangement of L4 and E3, sequence homology is not strong. For one of ordinary skill in the art to determine whether E3 (or which part of E3) is non-essential would require additional confirmatory experiments. (Ex. 2030 Kleibocker (1994); Ex. 2003 at page 4, lines 25-29; Ex. 2022 Reddy (1995) at page 100).

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human adenoviruses. Rather, E3 overlaps L5 in PAV3. (Ex. 2009 Spindler Decl. at ¶ 48 (*citing* Ex. 2022 Reddy et al (1995))).

116. Johnson claim 30 specifies that the insertion should be made between 81-84 map units of PAV3. (Ex. 2009 Spindler Decl. at ¶ 6 (*citing* Ex. 2005 Declaration of Interference mailed October 19, 2005)).

117. The AU patent application nowhere discloses map units 81-84 of PAV3 (Ex. 2003).

118. The AU patent application nowhere correlates map units 81-84 of PAV3 with the E3 region (Ex. 2003).

119. Three map units (81-84) of PAV3 in accordance with the 34.8 kb size of the PAV-3 genome specified in the AU patent application corresponds to 1044 base pairs. The AU patent application nowhere discloses which 1044 base pairs of the 1618 bps of the E3 region disclosed in Figure 5 corresponds to the 3 map units corresponding to map units 81-84. (Ex. 2003 at page 15, line 11).

120. The only map units disclosed in the AU Application are 97-99.5 map units at the right hand end of the genome. (Ex. 2003).

F. The Disclosures in the PCT application (Ex. 2004)

121. The description and figures of the PCT application were further amended under Rule 26 on November 11, 1999 to include additional and amended disclosure and figures. (Exs. 2004 and 2034.)

122. The *amended* version of the PCT application (Ex. 2034) entered the U.S. national phase under Rule 371 as Johnson's application-in-interference No. 09/485,512 ("the '512 application"), filed May 5, 2000. (Ex. 2002).

G. Priority accorded the Reddy provisional patent application (Ex. 2007)

123. The earliest constructive reduction to practice accorded to Reddy in the Declaration of Interference was U.S. Provisional Application No. 60/081,882 (Ex. 2007 "the '882 application"; Ex. 2005 Notice Declaring Interference, at page 3.)

124. The Reddy patent-in-interference No. 6,492,343 issued December 10, 2002 (Ex. 2001) is based upon U.S. Application Ser. No. 09/292,034, filed April 14, 1999 and claims priority to the '882 application (Ex. 2007.)

H. Persons Of Ordinary Skill In The Art

125. The art relevant to the technology at issue in this interference is the preparation of animal adenovirus-based vectors for administration to mammals. (Ex. 2009 Spindler Decl. at ¶ 9).

126. A person having ordinary skill in this art in 1996-1999 would have had at least a Master's degree in the biological sciences and/or a Bachelor's degree with at least two years of experience in adenoviruses and have been familiar with scientific and technical publications concerning animal adenoviruses and in particular, porcine adenoviruses. (Ex. 2009 Spindler Decl. at ¶ 9).

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Michael F. Borun
MARSHALL, GERSTEIN & BORUN LLP
6300 Sears Tower
233 South Wacker Drive
Chicago, IL 60606-6357
Tel: (312) 474-6300
Fax: (312) 474-0448

Date: February 24, 2006

By: _____
Evelyne Guillouet